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CLINICAL INVESTIGATION

Plasma concentrations and transperitoneal transport of native insulin and C-peptide in patients on continuous ambulatory peritoneal dialysis

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Plasma concentrations and transperitoneal transport of native insulin and C-peptide in patients on continuous ambulatory peritoneal dialysis. The insulin and C-peptide response to glucose (50 g), given intraperitoneally or enterally, and the elimination rate of these compounds has been studied in five nondiabetic patients on continuous ambulatory peritoneal dialysis (CAPD). The fasting C-peptide concentrations were three to ten times the normal values, whereas the fasting plasma insulin concentrations were within normal limits. After intraperitoneal glucose administration, a more marked hyperglycemia ($P < 0.05$) and a more long lasting hyperinsulinemia ($P < 0.05$) were found than after the enteral glucose load. The relative change in plasma C-peptide was slower and less pronounced in both experiments. Estimated total body clearance (K_t) for insulin was higher than for C-peptide ($P < 0.01$), but dialysis clearance (K_d) for C-peptide was higher than for insulin in both experiments ($P < 0.01$). The markedly elevated fasting C-peptide concentrations in plasma can be explained only partly by the absence of normal kidney function and suggests a continuously increased production of C-peptide during CAPD treatment. This was not reflected by the fasting plasma insulin concentrations. C-peptide measurements in plasma and dialysate during CAPD could be helpful in evaluating the β-cell function in patients in need of exogenous insulin.

Concentrations plasmatiques et transport transpéritonéal de l'insuline native et du peptide-C chez des malades en dialyse péritonéale continue ambulatorie. La réponse de l'insuline et du peptide-C à du glucose (50 g) donné par voie péritonéale ou parentérale et la vitesse d'élimination de ces substances ont été étudiées chez cinq malades non-diabétiques en dialyse péritonéale continue ambulatoire (CAPD). Les concentrations de peptide-C à jeûn étaient de trois à dix fois les valeurs normales, tandis que les concentrations d'insuline plasmatique à jeûn étaient dans les limites de la normale. Après administration intrapéritonéale de glucose, une hyperglycémie plus marquée ($P < 0,05$) et une hyperinsulinémie plus prolongée ($P < 0,05$) qu'après une charge glucosée parentérale ont été trouvées. Le changement relatif du peptide-C plasmatique était plus lent et moins prononcé au cours des deux expériences. La clearance totale estimée (K_t) de l'insuline était plus élevée que pour le peptide-C ($P < 0,01$), mais la clearence dialytique (K_d) du peptide-C était plus élevée que celle de l'insuline dans les deux expériences ($P < 0,01$). L'élévation marquée des concentrations de peptide-C à jeûn dans le plasma ne peuvent qu'être partiellement expliquées par l'absence de fonction rénale normale, et elle suggère une production augmentée de façon continue du peptide-C pendant le traitement par la CAPD. Cela n'était pas reflété par les concentrations d'insuline plasmatique à jeûn. Les mesures de peptide-C dans le plasma et le dialysat en cours de CAPD pourraient être utiles pour évaluer la fonction des cellules-β chez des malades ayant besoin d'insuline exogène.

Earlier investigations have provided information concerning the transport of exogeneous insulin from the peritoneal dialysate to plasma [1], but comparable data for transport of the endogenous hormone and the connecting peptide (C-peptide) from plasma to dialysate have not been published.

Insulin and C-peptide, which has no recognized metabolic activity, [2, 3] are produced in the pancreatic β-cells by cleavage of proinsulin and subsequently secreted into portal circulation in equimolar concentrations [4]. The liver removes about 60 to 70% of the insulin [2, 3], but only minor fractions of the C-peptide [2, 3]. It has been suggested that C-peptide is metabolized mainly by the kidney [2]. Normally, 5 to 20% of pancreatic secretion of C-peptide and 0.1% of endogenous insulin is excreted in urine [2, 4]. Half-time disappearance rates are about 11 to 33 min for C-peptide and about 5 min for insulin [2, 4, 5]. In the fasting state, the molar concentration of C-peptide in blood is five to seven times higher than that of insulin because of the slower turnover of C-peptide. After stimulation, the relative increase in insulin concentration is higher than for C-peptide, because of its lower basal concentration [2].

The β-cell secretory activity can be evaluated by measuring C-peptide concentrations in plasma and urine, also in insulin-treated diabetic patients [5, 6]; C-peptide measurements in plasma and dialysate during CAPD could be of value as an indicator of the β-cell function in patients on CAPD-treatment.

Transperitoneal glucose administration would be expected to give a response similar to intravenous glucose loading, but, to our knowledge, no data on differences in plasma glucose level and insulin response between oral and transperitoneal glucose loads have been published.

The purpose of this study was to investigate the plasma glucose, insulin, and C-peptide responses to equimolar glucose loads given either the peritoneal route or the oral route, and the total elimination and transperitoneal transport of these compounds in patients on CAPD treatment.

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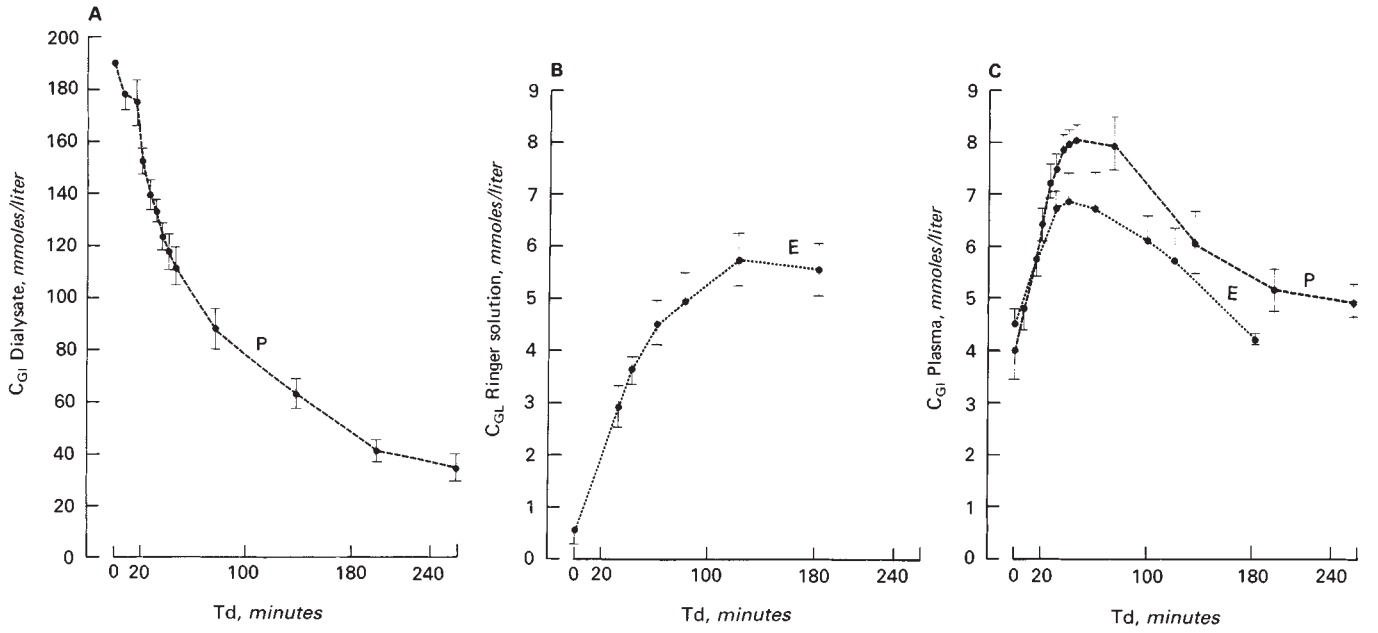

Fig. 1. *Glucose concentrations* (C_{GI}) *in dialysate* (**A**) *and instilled Ringer solution* (**B**) *and plasma* (**C**) *as a function of dwelltime* (T_d) *during peritoneal* (P) *and enteral* (E) *glucose load.* Mean ± SEM from five patients.

Methods

Patients. Five patients with the mean age of 44 years representing 21 to 57 years were selected for the investigation after informed consent was given. Two patients suffered from chronic glomerulonephritis, one from renal amyloidosis secondary to rheumatoid arthritis, one from juvenile medullary cystic disease, and one from renal failure due to lecithin-cholesterol acyltransferase (LCAT) deficiency. One patient was anephric, the others were anuric or oliguric. All patients had been well controlled on CAPD treatment for 3 to 16 months. The exchange procedure for all patients was four 2-liter bags per day, that is, three 5-hr shifts during the day and one 9-hr shift during the night. The mean blood values (± SEM and range) from six to ten consecutive measurements during this period were: hemoglobin, 9.5 ± 0.5 g/dl (8.2 – 10.8); glucose 5.6 ± 0.2 mmoles/liter (5.3 – 6.4); albumin, 28 ± 2 g/liter (21 – 33); and creatinine, 849 ± 88 μmoles/liter (553 – 1053).

Procedure of investigation

Each patient was examined twice with a 1-week interval.

Experiment 1. A peritoneal glucose infusion of 429 mmoles (77 g) was given using 2-liters of dialysate containing 3.86 g glucose/dl (Dianeal®, Travenol Industries, Halden, Norway). Simultaneous blood and dialysate samples for measurements of insulin, C-peptide, and glucose concentrations were taken before the instillation of fluid, and at the subsequent dwelltimes (T_d): 7 (during infusion), 15 (end of infusion), 20, 25, 30, 35, 40, 45, 75, 135, 195, and 255 (end of drainage) min after the start of dialysate infusion.

Experiment 2. Anhydrous glucose, 278 mmoles (50 g), dissolved in 75 ml water (corresponding to the mean 3 hr transperitoneal absorption of glucose during the first investigation, see Fig. 1A) were given by mouth while 1 liter of Ringer lactate (Knut Spaerens Laboratories A/S, Tønsberg, Norway) was instilled in the peritoneal cavity. Samples from blood and the instilled Ringer solution were obtained at the start and then at the following dwelltimes: 30, 40, 60, 80, 120, and 180 min (during drainage). Drained dialysate volumes were measured in both experiments.

All tests were begun in the morning, and the patients fasted during each investigation period. During the night before the test, 2-liters of dialysate containing 1.5 g glucose/dl were instilled for 9 hr. The peritoneal cavity was drained just before the investigation began the next morning.

Concentration measurements and kinetic calculations

Glucose concentration was measured using the oxidase method (Gluc-DH-Method, Merck, Darmstadt, West Germany), serum creatinine by an autoanalyzer (SMA III, Technicon Instruments Corporation, Tarrytown, New York), hemoglobin by a Coulter F analyzer (Coulter Electronics Lim, Harpenden, United Kingdom) and albumin by determination with bromcresol purple.

C-peptide concentrations were determined by a commercial RIA-kit ("C-peptide II kit," Aiichi, Tokyo, Japan). The WA-CV was 4.1% and the BA-CV was 4.3% within the range of 666 to 66600 pmoles/liter. Insulin concentrations were measured by a commercial RIA-kit ("Phadebas Insulin Test," Pharmacia, Uppsala, Sweden). The WA-CV 7.1% and the BA-CV was 6.5% within the range of 73 to 730 pmoles/liter.

As shown by Toffolo et al [7], the calculation of total body clearance (K_t) for insulin and C-peptide was based on a single compartment model with first order disappearance kinetics (that is, constant K_t), where insulin delivery rate (IDR = "production") can be simulated as:

$$IDR = k \cdot (C_g - h) \cdot t \text{ if } C_g > h, \text{ and } IDR = 0 \text{ when } C_g < h \quad (1)$$

C_g represents glucose concentration in plasma; h, given thresh-

old level of glucose for insulin stimulation; t, time; and k, individual constant. Values for "K_t" were based on $C_g < h$, giving IDR = 0, hence

$$\frac{d(C \cdot V)}{dt} = -K_t\, C \text{ giving } K_t = \frac{V}{T} \ln\left(\frac{C_o}{C_t}\right) \text{ for } C_g < h. \quad (2)$$

C represents the concentration in plasma and T, time. Distribution volume (V) was chosen as 16% of body wt [8].

The calculation of dialysis clearance (K_d) for insulin and C-peptide must be referred to the plasma concentration of these compounds, and we chose to use estimated mean plasma values ($\bar{C}_p$) during each of the two experiments as:

$$\bar{C}_p = \frac{1}{T}\int_0^T C_p \cdot dt \approx \frac{1}{T}\sum_{n=1}^{N-1} \bar{C}_n \cdot \Delta t_n;\ \bar{C}_n = (C_{n+1} + C_n)/2;$$

$$\Delta t_n = t_{n+1} - t_n \quad (3)$$

which gives a dialytic clearance as:

$$K_d = \frac{(V_d \cdot C_d - (V_{d0} \cdot C_{d0})}{\bar{C}_p \cdot T}. \quad (4)$$

For calculation of K_t and K_d, 4 hr were used in experiment 1 and 3 hr in experiment 2.

Statistical calculations were based on a paired *t*-distribution test of the differences between two populations. All values are given as mean ± SEM.

Results

The mean (± SEM) drained volume for all patients from the peritoneal cavity was 2810 ± 49 ml after 4 hr dwelltime during experiment 1, and 776 ± 47 ml after 3 hr dwelltime during experiment 2.

Figure 1**A**, **B**, and **C** depicts the relationship between the glucose concentration in the instilled peritoneal fluids and in blood as a function of time. Values from enteral (E) and peritoneal (P) glucose administration for both compartments are shown. During the first experiment, the measured mean glucose concentration in the 2 liters of instilled dialysate decreased from 190 ± 8.7 mmoles/liter to 40 ± 4 mmoles/liter after 3 hr. The ultrafiltration volume was about 0.8 liter, which corresponded to a mean glucose absorption of 268 mmoles (48 g) (Fig. 1**A**). The mean glucose loss from plasma to the Ringer solution during the second experiment was less than 6 mmoles (Fig. 1**B**).

The maximal increase in blood glucose after enteral ingestion of 50 g glucose was lower ($P < 0.05$) than during peritoneal absorption of glucose. After 3 hr of dwelltime, a slight difference in blood glucose concentration still existed ($P < 0.05$, Fig. 1**C**).

In Figure 2 changes in plasma insulin concentration are given as a percent of the initial fasting values (ΔC%). In both experiments, plasma insulin increased to about four times the initial values, but the increase in insulin concentration was more rapid during enteral than during the peritoneal absorption of glucose; however, the mean increase during 3 hr (based on the area under the curve) was about 50% higher after the peritoneal than after enteral glucose load ($P < 0.50$). At 3 hr of dwelltime, the insulin concentration in plasma was still 100%

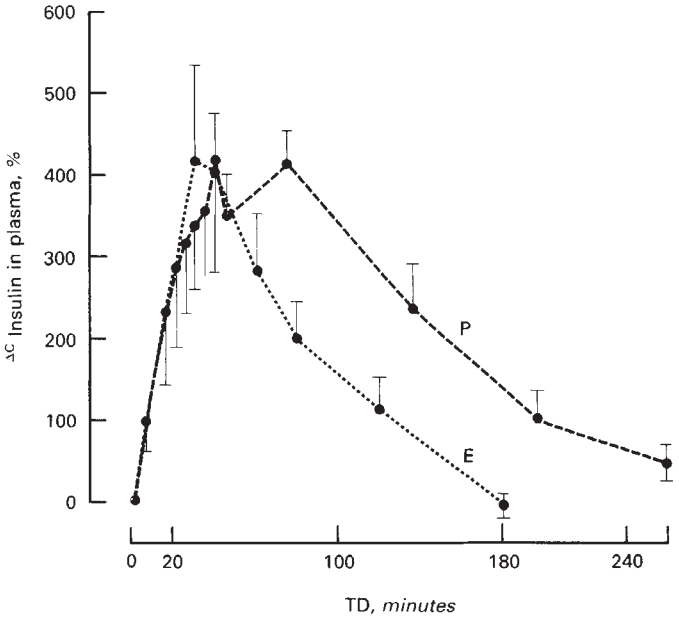

Fig. 2. *Relative change (in percent of initial values) in plasma insulin concentration, $\Delta C\% = (C - C_o)/C_o \times 100\%$, as a function of dwelltime (T_d) during peritoneal* (P) *and enteral* (E) *glucose load.* Mean ± SEM from five patients.

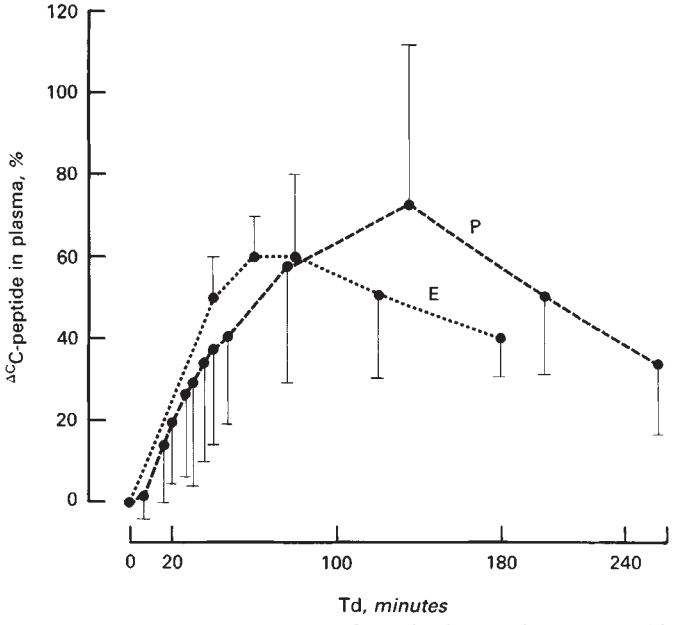

Fig. 3. *Relative change (in percent of initial value) in plasma C-peptide concentrations, $\Delta C\% = (C - C_o)/C_o \times 100\%$, as a function of dwelltime (T_d) during peritoneal* (P) *and enteral* (E) *glucose load.* Mean ± SEM from five patients.

increased after the peritoneal glucose load but normalized after enteral glucose ($P < 0.01$).

The relative change (ΔC%) in plasma C-peptide concentrations during the two experiments are compared in Figure 3. The increase in plasma values were slower and reached a level only about 70% higher than the initial concentration as compared to

Table 1. Lowest and highest values of insulin and C-peptide concentrations measured in plasma of each patient during peritoneal and anteral glucose loads

Patient no.	Enteral glucose load		Peritoneal glucose load	
	Insulin *pmoles/liter*	C-peptide *pmoles/liter*	Insulin	C-peptide
1	49 → 506	1665 → 3464	26 → 126	2398 → 4262
2	67 → 473	2198 → 4595	68 → 459	2364 → 4962
3	656 → 1467	8059 → 14119	274 → 1270	9491 → 11489
4	100 → 599	2930 → 4063	66 → 383	2498 → 4529
5	90 → 796	3796 → 5528	88 → 506	2997 → 5628
Mean range ± SEM	192 ± 116 → 768 ± 184	4330 ± 1020 → 6354 ± 1971	104 ± 44 → 557 ± 191	3950 ± 1390 → 6174 ± 1349
Normal values	0 to 511	376 to 909	—	—

400% for insulin (Fig. 2). The disappearance rate for C-peptide in plasma was also slower than for insulin. No significant differences between the two experiments were found.

Table 1 gives the lowest and highest values of insulin and C-peptide concentrations in plasma for each patient during the two experiments. The corresponding dwelltimes can be found by correlating these measured values with the time-dependent changes of these compounds shown in Figures 2 and 3. The concentrations of C-peptide were elevated compared to normal values, while fasting insulin levels were within normal range for all except one obese women (patient no. 3), who appeared to be hyperinsulinemic.

In Figure 4 the concentrations in the instilled fluid (C_d) relative to the mean plasma concentration ($\bar{C}_d$, see **Methods**) for insulin (**4A**) and C-peptide (**4B**) are given as a function of dwelltime (T_d). In both experiments the C-peptide concentration increased more than the concentration of insulin. During the peritoneal glucose load, the initial insulin values in the instillate increased rather irregularly and exceeded those of C-peptide, but for $T_d > 45$ min, the increase of both substances followed a simple diffusional behavior. After 3 hr of instillation time, the insulin concentration in the instilled fluids was 25.5 ± 8.6% (P) and 26.5 ± 2.3% (E) of mean plasma concentration ($\bar{C}_p$) respectively. The corresponding C-peptide concentrations were 35.4 ± 3.6% and 50.8 ± 6.8%.

Calculated mean total body clearance (K_t) and dialysis clearance (K_d) for insulin and C-peptide for the two experiments are shown in Figure 5, and the following differences should be noted: *(1)* Estimated K_t for insulin was higher than for C-peptide ($P < 0.01$), while K_d for C-peptide was higher than for insulin ($P < 0.01$) in both experiments. *(2)* When changing from 1-liter Ringer solution to 2-liter 4.25% dialysate in the peritoneal cavity, K_d for insulin increased from 1.13 ± 0.10 to 2.75 ± 0.64 ml/min ($P < 0.05$) and for C-peptide from 2.22 ± 0.40 to 4.35 ± 0.40 ml/min ($P < 0.01$). K_t for insulin decreased from 208.0 ± 39.8 ml/min during enteral to 117.2 ± 13.2 ml/min during peritoneal glucose load ($P < 0.025$) while K_t for C-peptide was unchanged in the two experiments, that is, 28.6 ± 6.0 and 28.1 ± 2.7 ml/min.

Discussion

The relatively rapid and complete absorption of glucose from duodenum and upper jejunum is due to both energy-dependent transport against a concentration gradient and diffusive transport [9]. Transperitoneal glucose absorption, however, appears to be simple diffusive and convective processes dependent only on individual differences in the peritoneal membrane permeability and the concentration gradient [1]. Peritoneal absorption takes longer time than intestinal absorption. To absorb a dose of 50 g glucose from an intraperitoneal pool of about 70 g (measured value) in 2 liters, 3 hr of dwelltime were needed (Fig. 1). The individual variability in absorption following this route of administration was about 30%. A more pronounced initial and longer lasting hyperglycemia was found when glucose was given through the peritoneal membrane (Fig. 1), and after 1 hr all patients remained more hyperinsulinemic during the peritoneal glucose load (Fig. 2).

The lasting hyperglycemia and hyperinsulinemia after peritoneal glucose administration can be explained by the slow and continuous absorption of glucose together with peripheral carbohydrate intolerance in uremic patients [10, 11]. The different initial hyperglycemia (0 to 45 min) in the two experiments can be due to differences in both glucose absorption and transport to peripheral blood. However, it is difficult to depict differences in these mechanisms. More than 60% of orally ingested, highly concentrated glucose solutions is absorbed within the first minutes [9, 12]. After intraperitoneal glucose administration, the glucose concentration decreased from about 190 to 110 mmoles/liter after 45 min. If the ultrafiltration volume at 45 min of dwelltime is estimated to be about 500 ml [1], calculated glucose absorption is 19 g. These findings, which agree with earlier measurements [1] contrast with the higher blood glucose levels found during peritoneal load in this study.

An explanation of the different degree of initial hyperglycemia in these experiments could be that a larger part of peritoneally absorbed glucose bypasses the portal circulation than does glucose absorbed from the intestine. It is uncertain from this study if the insulinotropic properties of gastric hormones [13] are of any importance in this matter.

The time-dependent relative changes in plasma C-peptide concentrations were slower and less pronounced than for insulin (Figs. 2 and 3). After stimulation, the C-peptide concentration in plasma was increased by 70% as compared to 400% for insulin. This is caused by the higher basal concentration of C-peptide [2], as the absolute increase in C-peptide values (pmoles/liter) (Table 1) was higher than that of insulin. The

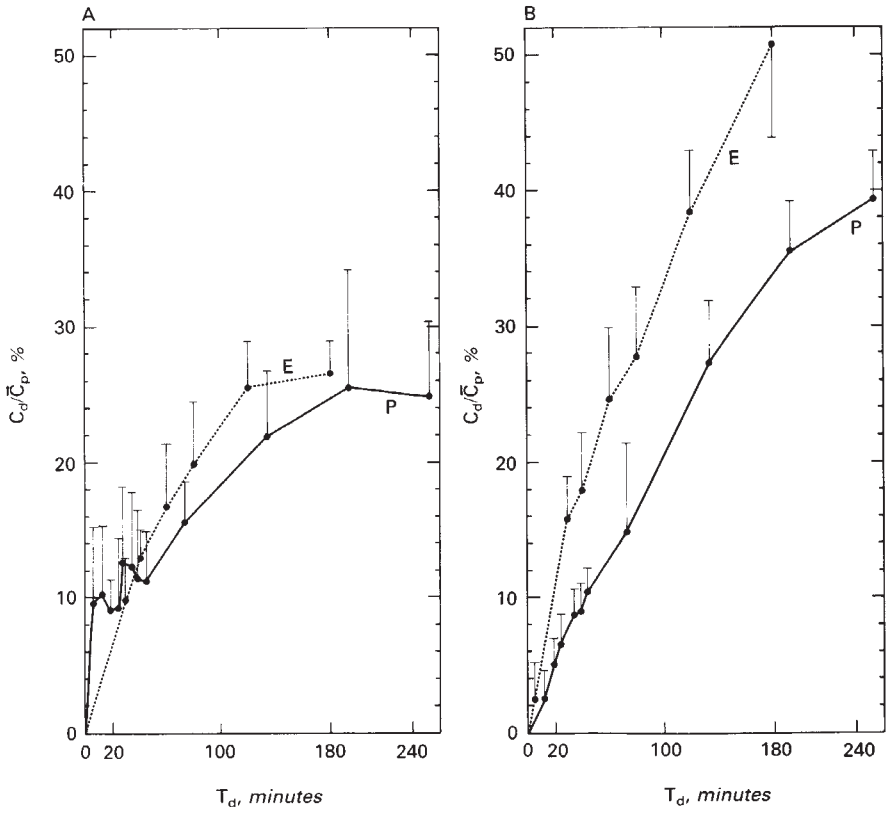

Fig. 4. *The concentration of insulin* (**A**) *and C-peptide* (**B**) *in instillate* (C_d) *relative to the calculated mean plasma concentration* ($\bar{C}_p$) *as a function of dwelltime* (T_d) *during peritoneal* (P) *and enteral* (E) *glucose load.* Mean ± SEM from five patients.

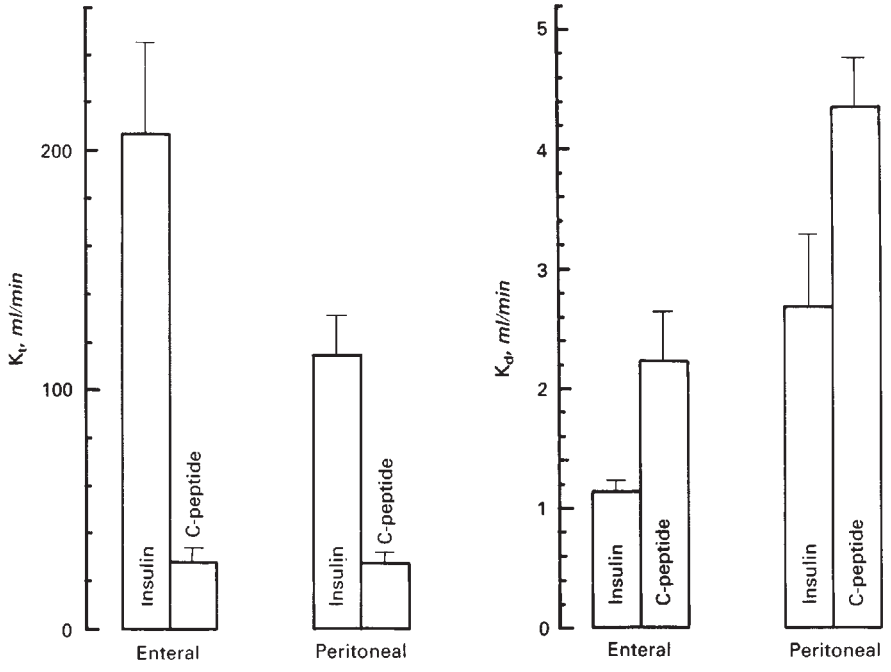

Fig. 5. *Calculated total body clearance* (K_t) *and dialysis clearance* (K_d) *for insulin and C-peptide during peritoneal and enteral glucose load.* Note the different scale for K_t and K_d. Mean ± SEM from five patients.

higher fasting values and slower disappearance rate for C-peptide are consistent with the lower hepatic and peripheral degradation rate found for C-peptide as compared to insulin [2, 3].

Increased fasting plasma C-peptide concentration in patients with chronic renal diseases have been reported by other investigators [14]. It was assumed that this elevation was attributed mainly to the failure of the diseased kidney either to degrade C-peptide or to excrete it into the urine, and to the state of uremia resulting in increased production of C-peptide. Increased molar ratio between fasting plasma C-peptide and insulin in uremic patients is also reported [14]. Our study confirms these findings;

however, both the fasting concentrations in plasma of C-peptide and the ratio between C-peptide and insulin were much higher than those found by other investigators in uremic patients treated with hemodialysis [14]. This could indicate that CAPD treatment results in a continuously increased production of proinsulin. This assumption could not be reflected by measurement of fasting insulin concentrations which were within the normal range.

After 4 hr of instillation of 2-liter hypertonic dialysate, the concentration in the instilled fluid relative to their mean plasma values, was about 25% and 39% for insulin and C-peptide, respectively (Fig. 4). These values are also reflected in the significantly higher K_d for C-peptide than for insulin (Fig. 5) and is probably due to the different molecular weights of insulin (~6000 daltons) and C-peptide (~3000 daltons). As expected from simple diffusion and convection, increased dialysate volume and osmolality resulted in increased K_d for both hormones (Fig. 5). Consistent with previous findings in diabetic and nondiabetic patients with normal renal function [2, 5, 6, 8], we found a significantly higher K_t for insulin than for C-peptide, reflecting the higher metabolic clearance [2, 3]. The lower K_t for insulin during the peritoneal glucose load compared to the enteral glucose load can be explained by the model used for calculation of K_t. Continuous glucose absorption through the peritoneum gives a sustained insulin secretion which causes the calculated clearance for insulin during peritoneal glucose administration to be underestimated as the formula used does not assume insulin production. The value for dialytic clearance of endogenous insulin was slightly higher than that previously found for (^{125}I)-labelled insulin administered into the peritoneal cavity (2.3 ml/min) [1], and these small differences have previously been explained to be caused by convective effects [15].

In conclusion, measurements of the time-dependent changes in plasma C-peptide concentrations after stimulation were not so sensitive as that of plasma insulin concentrations, but the three to ten times increased fasting C-peptide values in plasma assumes a continuous increased production of proinsulin during CAPD treatment. C-peptide concentrations in samples from instilled dialysate give a better estimate of plasma levels than corresponding insulin values. Measurements of C-peptide in both plasma and in the instilled peritoneal dialysate could be of value for an evaluation of β-cell function in patients on CAPD treatment needing exogeneous insulin and producing antibodies to this exogeneous compound.

Our experiments also show that the peritoneal route results in more prolonged hyperglycemia and hyperinsulinemia than the enteral. As insulin augments the hepatic production of triglycerides and very low density lipoproteins [16], this may contribute to a higher risk of progressive atherosclerosis in patients treated with CAPD. Substantiation of this is found in the preliminary findings of higher triglyceride levels in nondiabetic than in diabetic patients on CAPD treatment [17]. Long-term observations on changes in insulin response during CAPD treatment are still lacking.

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